

AREA OF EMPHASIS:

Women and Girls

SCIENTIFIC ISSUES

Although relatively few women were diagnosed with HIV/AIDS early in the epidemic in the United States, cumulative data through 2003 indicate that women make up an increasing proportion of the HIV/AIDS epidemic. According to the Centers for Disease Control and Prevention (CDC), by the end of 2003 women accounted for an estimated 22 percent of adults and adolescents living with AIDS in the United States, increasing from 14 percent in 1992. CDC data indicate that between 1999 and 2003 the annual number of estimated AIDS diagnoses increased 15 percent in women as compared with 1 percent in men. In 2003, 27 percent of newly diagnosed AIDS cases were among women. Women accounted for 16 percent of the cumulative AIDS deaths reported in the United States through 2003, and in 2003 represented 26 percent of reported AIDS deaths. According to CDC data from 2000–2003, 78 percent of women acquired HIV through heterosexual sex and 19 percent were infected through injecting drug use.

HIV/AIDS affects women of all ages in the United States, but it is most prevalent among women in their childbearing years. CDC data from 2000–2003 indicate that 61 percent of female AIDS cases occurred in women between the ages of 25 and 44 years. In 2003, among persons aged 13–24 years, females accounted for 41 percent of reported HIV/AIDS cases.

Members of racial and ethnic minority communities bear a disproportionately greater burden of the HIV/AIDS cases among women in the United States. According to the CDC, from 2000–2003 rates of HIV/AIDS diagnoses among African American women were 19 times greater than those among white women and together African

American and Hispanic women comprised approximately 80 percent of HIV/AIDS diagnoses. In 2003, the rate of AIDS diagnoses for African American women was approximately 25 times the rate for white women and 4 times the rate for Hispanic women. Of newly diagnosed women in 2003, approximately 67 percent are African American, 18 percent are white, 17 percent are Hispanic, and a small percentage are Asian/Pacific Islander or American Indian/Alaska Native.

Globally, women and girls comprise approximately 50 percent of those with HIV infection, according to a Joint United Nations Programme on HIV/AIDS (UNAIDS) report from the end of the year 2004. While rates of HIV/AIDS vary according to geographic area, the majority of infected women around the world are of childbearing age. Most women become infected through heterosexual intercourse. In some geographic areas, a significant proportion contract HIV infection through injecting drug use or high-risk sex associated with drug use. Mortality rates for women with HIV/AIDS continue to rise worldwide.

Factors driving the epidemic in women are complex and are related to both gender and sex. In several respects, women experience HIV/AIDS differently from men. In addition to greater biologic susceptibility to infection and lack of highly effective female-controlled barrier methods to prevent heterosexual acquisition, associated sociocultural and behavioral factors such as disempowerment, domestic or partner violence, economic dependence, reproductive expectations, poor self-efficacy for negotiating safer sex in male-female relationships, and AIDS-related stigma all confer vulnerability to HIV/AIDS throughout the life course. Additionally, although advances in AIDS medications have reduced AIDS-related mortality in the developed world, studies indicate that use of antiretroviral (ARV) medications among HIV-infected women is lower than among men, and women overall have received less benefit from new therapies as compared with men. One of the key issues in the diagnosis, care, treatment, and prevention of HIV infection for women and girls is access to health care resources. In the United States, research has shown that HIV-infected women encounter more barriers to care and are diagnosed and enter health care services generally at later stages of infection than do men. Because they tend to be poorer and have dependent children, women with HIV/AIDS who are receiving care are nearly twice as likely as men to be covered by Medicaid and half as likely as men to be privately insured. About 20 percent of HIV-infected women are uninsured altogether. A higher proportion of women than men with HIV infection report postponing medical care for themselves due to such barriers as sickness or lack of transportation. When they do receive care, women with HIV/AIDS fare more poorly than do men on a number of access and quality measures. For example, HIV-infected women are more likely to be hospitalized and use the emergency room, and are less likely to receive highly active antiretroviral therapy (HAART) than are men. In addition to systems barriers, adherence to and maintenance of treatment and care are often complicated by individual life circumstances, such as

substance abuse or mental health issues. In many international settings, access and availability of care are lacking or cultural stigma inhibits diagnosis and utilization of treatment. Better understanding of sex and gender issues is critically important to development of effective interventions to prevent HIV acquisition and reduce HIV-related morbidity and mortality.

PRIORITY FOR FUTURE RESEARCH:

- **Study the biology of the reproductive tract and mucosal surfaces of HIV-infected and HIV-uninfected women and girls, integrating studies of physiology, pharmacology, immunology, microbiology, and anatomy in order to clarify mechanisms of HIV transmission, acquisition, and disease progression.**

There are many questions that remain unanswered regarding specific anatomical and physiological characteristics of women and girls that play a role in transmission, acquisition, or resistance to HIV infection. Better understanding of the biology of HIV transmission in women and girls requires investigating the molecular basis and chronology of the early steps in the infectious process, including identification of cells susceptible to HIV infection in the lower and upper reproductive tract; the vaginal and cervical ecology; the natural and acquired defense mechanisms at those mucosal sites; and the role of viral load in HIV transmission. Other important factors in HIV acquisition may include the influence of hormonal modulation on viral replication and immune responses in the reproductive tract, and cofactors such as coincident infections with other sexually transmitted disease (STD) pathogens. Understanding the complex factors associated with HIV acquisition relative to different sites of exposure is essential to development of a vaccine that is effective for women.

PRIORITY FOR FUTURE RESEARCH:

- **Elucidate a range of innate and acquired host characteristics and viral interactions through the course of HIV infection (in particular, during primary HIV infection and response to treatment) across the life cycle in women and girls.**

While basic mechanisms of viral replication and pathogenesis may not differ significantly in women and men, research has shown that there are sex differences in the way HIV disease interacts with its host through the course of HIV infection. Studies have highlighted differences in viral dynamics in women compared with men. HIV viral load has been found to be lower in women than in men immediately after seroconversion, with a narrowing of the differences with increasing duration of time since infection. Differences in CD4 lymphocyte counts have also been observed, with some data indicating that women have a steeper decline than men. The mechanisms underlying these observations are unclear but may be

related to hormonal influences. Recent data suggest differences in cellular markers in adolescent girls as compared to boys, as well as between pre- and postmenopausal HIV-infected women.

PRIORITIES FOR FUTURE RESEARCH:

- **Develop and continue domestic and international clinical studies — biological, therapeutic, vaccine, natural history, epidemiological, behavioral, and social — to ascertain the effects of sex and gender in HIV infection and response to treatment among women and girls.**
- **Power clinical trials to identify sex and gender differences.**

Further research is necessary to understand important sex and gender differences that have been observed in the manifestations of HIV disease and as consequences of HIV therapy. It is important to further characterize these differences and the effects of long-term therapy across the life cycle, including among adolescent girls and peri- and postmenopausal women. One significant area for continued research is the metabolic abnormalities and body composition changes associated with HIV infection, disease, and treatment. Although the incidence of wasting has declined as a result of effective antiretroviral therapy (ART), wasting, which is characterized by weight loss and malabsorption, remains a major cause of morbidity and mortality in individuals who do not respond or lack access to anti-HIV treatment. Women exhibit a disproportionate decrease in body fat relative to lean body mass both at early and at advanced stages of wasting, while men experience a disproportionate decrease in lean body mass and a relative sparing of body fat. Insulin resistance, hypercholesterolemia, hypertriglyceridemia, and abnormal fat redistribution (either depletion or accumulation) have been described in HIV-infected individuals taking ART. In addition to the direct effect of the drugs, the following may play a role in the development of these abnormalities: age, duration of therapy, stage of HIV infection and disease, and return to health following suppression of viral replication. For women, the fat redistribution tends to be away from the face, limbs, and buttocks, and toward breasts and stomachs, an occurrence that is both physically and psychologically detrimental.

Of major concern are a number of HIV-related conditions that relate to gynecological manifestations, especially vulvovaginal candidiasis, pelvic inflammatory disease, and cervical dysplasia. HIV-infected women are at greater risk for cervical human papillomavirus infection, which has been associated with cervical cytological abnormalities. Other common HIV disease manifestations among women include oral and esophageal candidiasis, herpes simplex virus infection, and cytomegalovirus infection. Additional research is necessary to better understand the biological underpinnings and consequences of these clinical manifestations,

as well as their relationships to HIV disease, other cooccurring conditions, and therapeutic interventions utilized by women and girls. As more women remain on long-term HIV therapy, better understanding of the intersection of HIV, ART, and the chronic conditions associated with aging, such as neuropsychological status and cardiovascular disease, is necessary to improve clinical management and disease outcomes.

Research analyses regarding differential rates of HIV/AIDS disease progression and death between women and men have focused scientific investigations on sex- and gender-related differences in response to therapy. A key question is whether ART regimens need to be different for women and men. So far, in population-based cohort studies assessing virologic, immunologic, and clinical outcomes, research has not shown sex-based differences in overall treatment effectiveness. However, current ARTs, alone and in combination, have side effects and toxicities, some of which may be sex-specific. Some research indicates that women who take nucleoside analogue reverse transcriptase inhibitors are more likely than men taking these drugs to experience adverse events, including neuropathy and pancreatitis, which have resulted in toxicity-driven changes in ART regimen. Studies indicate that women are more likely to experience side effects, such as rash, from nevirapine than are men, and in women, protease inhibitor use results in higher drug concentrations than in men at the same dose, which can result in allergic reactions and gastrointestinal symptoms. Further research is necessary to determine the bases of sex and gender differences, such as hormonal influences, in response to therapies. Particular attention needs to be paid to sex-based differences in ART pharmacokinetics, pharmacodynamics, and pharmacogenetics. In addition, many HIV-infected women take ART medications in combination with other drugs—legal and illicit. There are data to suggest that some ART agents interact with oral contraceptives, diminishing the effect of the contraceptives. Additional research is needed on the potential interactions between ARTs and other medications used by women, including medications for opportunistic infections (OIs) and other comorbid conditions prevalent in women, as well as between ARTs, alcohol and illicit drugs such as heroin, cocaine, and methamphetamines, and the pharmacotherapies used to treat those conditions. (*Note:* Please see the Natural History and Epidemiology and Therapeutics Areas of Emphasis in this Plan for further details.)

Much of the research on women has been focused on HIV-infected pregnant women and mother-to-child transmission (MTCT). (*Note:* In this section of the Plan, issues of MTCT are included to the extent that the focus is on the pregnant or postpartum woman, rather than the child. More detailed discussions of prevention of perinatal transmission may be found in the Natural History and Epidemiology and Therapeutics sections of the Plan.) The preponderance of evidence to date suggests that pregnancy itself, including repeat pregnancies, does not exacerbate HIV disease progression in women. Currently, there are no major differences

in the recommended treatment regimens for pregnant and nonpregnant HIV-infected women, although treatments may be adjusted during different trimesters of pregnancy. Recent studies have demonstrated improved obstetric outcomes and few maternal toxicities associated with ART use during pregnancy. As efforts to prevent maternal-child transmission through ART use are expanded, much remains to be known about the impact of ART exposure during pregnancy, including the development of viral resistance.

Critical to improved medical management and outcomes for women and girls is the development of better structural and behavioral interventions that are integrated with biomedical interventions and appropriately responsive to the unique aspects of the disease in women and girls. While research has increased our understanding of behavioral and social correlates of successful treatment for HIV, interventions to improve access to, initiation of, and sustained adherence to therapy and medical care, in both domestic and international settings, are an urgent need.

Both long-term effectiveness and clinical trial efficacy studies are critical venues for improved treatment for women and girls. Analyses of sex and gender differences are critical to understanding success or failure of treatment modalities. To date, many clinical trials of HIV therapeutics have not had sufficient numbers of women to rigorously examine such differences. While women now constitute about 17 percent of NIH-sponsored clinical trial participants, which is close to the proportion of HIV infection in women in the United States, this number may not be large enough to allow for appropriate statistical analysis of sex and gender differences in any one trial. Recent vaccine trials, for example, have not had sufficient numbers of women enrolled to evaluate potential sex differences in vaccine response. As new therapeutic and vaccine products are developed, enhanced research efforts are needed to increase clinical trial participation among women and to integrate behavioral components into the clinical trials paradigm, in order to understand both biologic and behavioral elements influencing trial outcome.

PRIORITY FOR FUTURE RESEARCH:

- **Explore factors that influence development, adoption, use, and effectiveness of women-controlled methods (including physical and chemical barrier methods), alone or in combination, for preventing HIV transmission and acquisition.**

Improved understanding of the behavioral and social dynamics of sex and gender is essential to the design of effective HIV preventive interventions for women and girls. Such interventions must be not only gender-specific, but also culturally appropriate and acceptable. Most behavioral interventions involve developing a sense of self-efficacy and providing the skills necessary for women to negotiate with men about the use of condoms, particularly male condoms, or to abstain from sexual

intercourse. But these approaches are not necessarily appropriate or relevant to some cultural settings, where frank discussions of sex and sexuality and negotiation among women and men are not the accepted norm. Thus, other forms of HIV prevention for women are necessary, in addition to behavioral interventions. Increased attention has focused on female-controlled physical and chemical barrier methods that do not necessarily require negotiation with male partners for use during sexual intercourse to protect against HIV transmission and acquisition. The female condom is one physical barrier method, but this method has had mixed acceptability among women, chiefly because of its cumbersome design and administration. Research is underway to test the efficacy of diaphragms and cervical caps—currently used for contraception—for preventing HIV infection and other sexually transmitted infections (STIs).

A key focus of current NIH HIV prevention research is the development and testing of safe, acceptable, and accessible chemical barriers known as microbicides to prevent HIV transmission during sexual intercourse. Many compounds already have been screened and tested, and a number that have shown promise are in various stages of clinical trials. Researchers are addressing such issues as maintenance of normal vaginal pH and flora, ease of use, long-lasting effect, potential adverse effects on sperm and on integrity of mucosal tissue, and behavioral issues related to acceptability and use of microbicides in the context of sexual relationships. (*Note:* Please see the Microbicides Area of Emphasis in this Plan for further details.) It is essential that HIV prevention methods for women take into account women's reproductive interests. Physical and barrier methods for HIV prevention should be developed with both contraceptive and noncontraceptive properties to allow for the full range of women's reproductive choices.

PRIORITY FOR FUTURE RESEARCH:

- **Integrate basic behavioral and social science research (theoretical and methodological) on gender construction, maintenance, dynamics, and consequences—including gender-based stigma and discrimination—into the design and evaluation of HIV prevention and care interventions.**

In addition to biological differences, psychological factors, cultural attitudes, and social and economic position influence the causes and consequences of HIV/AIDS in women and girls. In many societies, women and girls hold lower social positions than men and boys, resulting in economic dependence, inequality in decisionmaking, poorer education, gender-related stigma, and less access to health care and other social supports. These factors can confer additional vulnerabilities to HIV infection and AIDS, and influence differential health outcomes for women and men. It is important to develop HIV/AIDS interventions that take into account the context of the socially constructed aspects of male and female relationships within various sociocultural settings. These relationships, governed by social and cultural norms,

may influence development of sexual and other behaviors and conditions that provide protection from or vulnerability to HIV/AIDS. The multiple determinants of sexual and other risk behaviors, such as substance use, occur along a developmental trajectory across the life cycle in the context of social arrangements that often are characterized by gender inequality and power imbalances. Such power imbalances may extend to intimate relationships between women and men that contribute to women's increased vulnerability to HIV/AIDS by inhibiting protective or health-seeking behaviors. In addition to intimate partner relationships, other significant relationships including family, children, and community members influence both HIV transmission risk behaviors and behaviors in response to the impact of HIV infection. Development of interventions that take into account the effects of culturally influenced gender roles and relationships on HIV-related behaviors is an important area of further study.

HIV-infected women encounter multiple psychological issues. In addition to coping with the disease itself, for many women underlying mental health issues, coexisting substance abuse, partner or family violence, lack of resources, and dependent children are factors that increase the burden of HIV/AIDS. Studies indicate that women with HIV infection and AIDS have a greater risk of psychiatric disorders, distress, and other mental health problems than do men. For some women, psychological distress and depression can influence ability to initiate and sustain HIV treatment and medical care, and can lead to use or abuse of alcohol and other drugs. Further research among girls and women needs to be undertaken in order to integrate understanding of the psychological impact of HIV across the life cycle, as physiologic and life circumstances change, into preventive and care interventions. In order to improve treatment and care outcomes, development is needed of effective interventions that take into account the psychological dynamics of asymptomatic infection and subsequent disease consequences, including reproductive choices, initiation and maintenance of HIV treatment, treatment for psychiatric illness or substance abuse, the impact of HIV therapy on body image and related stigma, quality of life, and primary caretaker self-efficacy. Gender differences in psychological stress relate to women's potentially stressful roles as primary caretakers in families, women's greater likelihood of being poor, and women's greater likelihood of being victims of abuse, including sexual assault. Women may also employ different coping skills than men, for example, discussing their problems with close relatives and friends, praying, expressing anger, and engaging in denial.

Utilizing basic behavioral and social science theory and methodology to further develop HIV prevention and care interventions, as well as to evaluate the efficacy and effectiveness of those interventions, will facilitate better integration of biomedical and sociobehavioral approaches to reducing HIV infection and HIV-related morbidity and mortality. (*Note:* Please refer to the Behavioral and Social Science Area of Emphasis of this Plan for more detailed discussion.)

PRIORITY FOR FUTURE RESEARCH:

- **Enhance opportunities and mechanisms for recruiting and training biomedical, behavioral, and social scientists in the conduct of interdisciplinary and multidisciplinary HIV/AIDS research in women and girls, addressing women's health issues and analyzing sex and gender differences, and facilitate development of the infrastructure to support such research.**

In order to develop more effective HIV/AIDS interventions for women and girls, it is critical to augment efforts to build interdisciplinary and multidisciplinary research capacity, both domestically and internationally, that encourages and supports research to further understanding of HIV/AIDS in women and girls. Training and mentoring opportunities for researchers from the disciplines of biomedical, behavioral, and social sciences will promote development of relevant scientific knowledge and the methodologic and analytic skills that can address the multifaceted nature of HIV disease in women and girls. Such interdisciplinary and multidisciplinary approaches can address important sex and gender differences in all aspects of HIV/AIDS science, and strengthen and facilitate integrated biomedical and sociobehavioral prevention interventions.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Elucidate biologic determinants of HIV transmission and define the mechanisms by which viral, host, and immune factors may influence the process of HIV transmission and acquisition among women and girls across the life cycle.

STRATEGIES:

- Evaluate HIV transmission and acquisition in relation to viral factors, such as genotype, phenotype (inclusive of drug resistance), clade, viral load, replicative forms, viral fitness, and heterogeneity.
- Identify and characterize cells responsible for viral acquisition and propagation at mucosal surfaces in the oral cavity and the entire reproductive tract (fallopian tubes, uterus, cervix, vagina, vulva) and anal canal.
- Evaluate HIV transmission and acquisition in relation to viral shedding in different mucosal compartments (including semen, cervicovaginal secretions, and saliva).
- Evaluate HIV transmission and acquisition in relation to age, timing, and occurrence of endocrine status changes (premenarche, menarche, postmenarche, pregnancy, premenopause, menopause, and postmenopause); the exogenous use of hormones for contraception, ovulation induction, and hormone replacement should be included.
- Over all age ranges, evaluate HIV transmission and acquisition in relation to normal vaginal (and oral) microflora and various infectious factors, such as STDs and preexisting local/systemic infections with other microbes.
- Evaluate HIV transmission and acquisition in relation to host genetic factors that influence susceptibility and resistance to infection.
- Elucidate mechanisms of innate immunity and other cellular factors affecting acquisition of HIV.
- Evaluate HIV transmission and acquisition in relation to other host factors, such as nutrition, nonhormonal contraception use, anatomic/physiologic changes (female circumcision, cervical ectopy, postdysplasia treatment), and localized inflammation secondary to use of intrauterine devices, local vaginal therapies, douches, or vaginal astringents.
- Study the biology of the systemic and mucosal immune system (innate and adaptive) in women and girls and the impact of HIV infection.

- Define how genetic, infectious, and endocrine factors alter local and systemic immune responses and the impact on HIV acquisition and transmission.
- Study the impact of effective ARTs on genital tract viral dynamics (including the development of resistance) and vertical and sexual HIV transmission.

To facilitate the research goals listed above:

- Develop standardized assays for immune response and viral load, as well as other relevant parameters, in genital tract and oral samples;
- Develop noninvasive procedures for genital tract sampling; and
- Promote studies in animal models to explain host-viral-immune factors involved in HIV transmission and acquisition.

OBJECTIVE - B:

Study the biology of HIV infection, progression to disease, and development and course of clinical manifestations associated with HIV infection, coinfections, and concomitant conditions among women and girls across the life cycle.

STRATEGIES:

- Elucidate the unique mechanisms mediating virus-host interactions in HIV disease progression among women and girls.
 - ▶ Evaluate HIV viral dynamics and replication in blood and at the tissue level and immune function among women and girls.
 - ▶ Determine normative values for immune parameters including total lymphocyte number, subset composition, and immune cell turnover and distribution and the impact of HIV infection across the life cycle.
 - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including hormonal endogenous factors (inclusive of hormonal changes across the life cycle and throughout the menstrual cycle) and exogenous factors (inclusive of hormonal contraception and hormonal replacement therapy); pregnancy; and autoimmune diseases.
 - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including infectious agents such as hepatitis C virus (HCV) and STIs; use and abuse of alcohol and other substances; reexposure to different strains of HIV including drug-resistant strains; age; intermittent therapy and monotherapy for perinatal transmission; and genetic factors.
 - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including nutrition, biological indicators of stress, drug use, and complementary and alternative medicine approaches, including herbal therapies and nutritional supplements.
- Develop approaches for identifying, recruiting, enrolling, and retaining recently exposed and newly HIV-infected women and girls for studies on the pathogenesis of HIV infection.
- Elucidate the unique etiologies and pathogenic mechanisms of disease manifestations in HIV-infected women and girls.
 - ▶ Investigate HIV- and therapy-associated metabolic and body composition changes that may be operative at various stages of infection and disease,

to include changes in fat distribution, bone density, menstrual function, fertility and sexual function, and cardiovascular disease.

- ▶ Conduct studies on the gynecologic manifestations and identification and treatment of gynecologic disease in HIV-infected women and girls.
 - ▶ Elucidate characteristics of OIs and coinfections in HIV-infected women and girls.
 - ▶ Elucidate characteristics of HIV-related malignancies, including female-specific cancers.
 - ▶ Investigate the impact of comorbid conditions on HIV-related manifestations in women and girls including HCV coinfection and autoimmune disease.
 - ▶ Elucidate characteristics of neurologic and neuropsychologic manifestations (dementia, changes in cognitive function) of HIV infection/disease in women and girls, including the role of potential cofactors such as substance abuse, mental health disorders, HCV infection, and preexisting neurological conditions.
 - ▶ Investigate clinical manifestations related to HIV and HIV-related therapies in pregnant and postpartum women, including toxicity (e.g., lactic acidosis, hyperglycemia) and peripartum/postpartum morbidity in HIV-infected women undergoing vaginal or operative delivery.
- Evaluate the impact of HIV and HIV-related therapies on breastfeeding.
 - Explore further the role of pharmacogenetic factors as explanations for variations in HIV disease course.

OBJECTIVE - C:

Conduct and support research to inform the diagnosis, care, and treatment of HIV-infected women and girls across the life cycle, including clinical studies of therapeutic interventions.

STRATEGIES:

- Evaluate innovative and rapid testing strategies in a range of settings to identify HIV infection in women and girls.
- Study the psychosocial consequences of receiving HIV-positive results on women across the lifespan, including during adolescence, during the reproductive years, and during menopausal and postmenopausal stages of life, and the impact on treatment and care decisionmaking.
- Evaluate the impact of antepartum treatment on the natural history of disease and development of viral resistance.
- Enhance efforts to evaluate the efficacy and effectiveness of new and existing therapies and therapeutic regimens across the life cycle, in both treatment-naïve and treatment-experienced women and girls.
- Study factors affecting adherence to HIV therapeutic regimens across the lifespan, and develop and evaluate focused interventions designed to improve adherence to HIV therapy.
- Evaluate the impact of non-HIV therapies and concomitant diseases, including substance abuse and mental disorders, on women's eligibility for participation in clinical trials, access to health care, and utilization of and adherence to treatment.
- Support research and development of clinical trial designs and statistical methodologies to evaluate clinical efficacy and reasons for success or failure of anti-HIV treatments among women and girls, including timing of treatment initiation, treatment interruptions and treatment cycling, treatment in the presence of other comorbid conditions, treatment during pregnancy, and the utility of surrogate markers.
- Conduct research to optimize diagnosis and treatment of comorbidities in women with HIV.
- Evaluate the interaction of mental health therapies and anti-HIV therapies on the course of disease progression.
- Evaluate short- and long-term toxicity, pharmacokinetics, and ARV activity of therapeutic agents in women across the life cycle, including during pregnancy.

- Investigate therapeutic interactions of anti-HIV medications with other medications used by women, including interactions of ARTs with therapies for OIs; therapies for illnesses that affect women specifically, disproportionately or differently from men; hormonal treatments; treatments for substance abuse; and complementary and alternative medicine approaches.
- Evaluate the long-term effects of anti-HIV therapy on morbidity and mortality among girls and women across the life cycle.

OBJECTIVE - D:

Conduct and support basic and intervention research to address the gender-specific, psychological, behavioral, social, environmental, economic, and cultural dynamics that increase or decrease risk for, and protection from, HIV transmission, acquisition, and disease progression among women and girls across the life cycle.

STRATEGIES:

- Examine the impact of population-level interventions on HIV acquisition among women and girls, such as social normative behavior changes, programs to increase educational opportunities and economic independence, mass or syndromic approaches to STI control, early diagnosis and treatment of HIV infection and other STIs, use of family planning programs to diagnose and treat STIs, and availability and access to substance abuse treatment.
- Support research across the life cycle that explores the impact of HIV risk perception on sexual activity decisionmaking, including decisions about pregnancy.
- Study how HIV-related risk and protective behaviors might change over time as a function of developmental and life-course events, such as adolescence, childbearing, sexual partnership choice and change, HIV treatment, menopause, and loss of family, social, and economic support.
- Support female-focused intervention research to prevent HIV acquisition through enhanced healthy sexual development and development of protective behaviors across the life course.
- Develop, implement, and evaluate interventions that address partnership issues regarding increased and decreased risk of HIV infection (e.g., dating, relationship violence, power in relationships, drug use, and economic survival sex).
- Develop innovative prevention strategies targeting male partners whose behaviors confer risk of HIV transmission to female partners, particularly in populations/areas with elevated HIV prevalence.
- Develop, implement, and evaluate culturally focused outreach and peer-based HIV prevention interventions that address risk behaviors and related perceptions of risk.
- Develop, implement, and evaluate prevention interventions for populations perceived to be at low risk for HIV infection, such as sexually active middle-aged and older women, college students, those with physical and mental disabilities, bisexual women and girls, women and girls residing in rural areas, Asian/Pacific Islanders, Native Americans, and Alaska Natives.

- Develop, implement, and evaluate culturally focused HIV prevention, treatment, and care interventions targeting populations of women and girls at risk due to vulnerable and/or isolating circumstances (e.g., orphaned, incarcerated, refugees, sexual exploitation, trauma, violence, war, homelessness, runaways, gang membership, alcohol and substance abuse).
- Support research to improve translation of effective culturally focused behavioral and social science-based HIV prevention, treatment, and care interventions to communities and health care and prevention service providers serving women and girls.
- Study the impact of macro events (e.g., natural disasters, trauma, war) on HIV risk for women and girls.
- Support HIV research focused on community-level factors (social, cultural, and gender norms and ideologies) that increase or decrease risk of HIV transmission and acquisition among women and girls.

OBJECTIVE - E:

Conduct and support basic and intervention research to develop, test, and evaluate safe and effective technologies and products, including vaccines and chemical and physical barrier methods that are appropriate, acceptable, and accessible to women and girls, for preventing transmission and acquisition of HIV.

STRATEGIES:

- Support the discovery, development, and preclinical evaluation of new, improved, acceptable, effective, and safe chemical and physical barrier methods, including topical microbicides and other methods, to reduce sexual transmission of HIV and STIs among women and girls.
- Support the evaluation of existing chemical and physical barriers to reduce sexual transmission of HIV and STIs among women and girls.
- Support the evaluation of the contraceptive efficacy of chemical and physical barrier methods and how the efficacy affects acceptability for use in HIV prevention.
- Identify populations of women and girls with HIV incidence levels suitable for recruitment into vaccine and other HIV prevention intervention trials.
- Develop and evaluate methods to access, recruit, and retain women and girls who are demographically representative of the populations at risk for HIV infection for preventive intervention studies (women and girls to include racial/ethnic minorities, adolescents, substance users, and the mentally ill).
- Develop and assess the effectiveness of utilizing multiple prevention approaches, both individually and in combination, that may decrease HIV transmission among women and girls.
- Develop and evaluate biomedical and behavioral interventions for managing STIs (including mass treatment or syndromic approaches) as a potential means of preventing HIV transmission and acquisition.
- Investigate candidate vaccines and other biomedical prevention strategies both in human subjects and in animal models of HIV infection with attention to factors particularly relevant to use in women and girls, such as changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormonal replacement therapy, and presence of selected STIs.
- Study potential effects of candidate vaccine or microbicial products on the genital tract immune system and their ability to induce inflammatory activity that might compromise the integrity of the mucosal surface of the genital tract and decrease or enhance the inductive ability of vaccines.

- Study the impact of biomedical interventions to prevent mother-to-child transmission, including caesarean section, on maternal morbidity and mortality.
- Support research to improve translation and dissemination and increase adoption of effective HIV prevention technologies by communities and by health care and prevention service providers who serve women and girls.
- Develop and evaluate innovative ways to obtain culturally and age-appropriate fully informed consent for participation in HIV prevention trials, and document critical aspects of informed consent (e.g., procedures, risks, benefits, voluntary nature, confidentiality, etc.).
- Support research to identify barriers to enrolling girls under 18 years of age in HIV prevention trials and to develop strategies for overcoming these barriers, including hard-to-reach populations such as girls living outside of family care, girls involved in the juvenile justice system, and substance abusers.

OBJECTIVE - F:

Conduct and support basic and intervention research on the biological, psychological, social, and economic consequences of HIV/AIDS for infected and affected women and girls.

STRATEGIES:

- Conduct multidisciplinary research to understand the synergistic effects of HIV-related disease progression and premorbid and comorbid clinical and psychosocial conditions affecting women and girls, and the mechanisms underlying these effects; develop interventions to enhance physical and mental health outcomes.
- Develop and evaluate interventions that target HIV-serodiscordant couples to prevent transmission and to promote coping and quality of life.
- Support research to understand the consequences of HIV infection and disease progression on women's and girls' sexual and reproductive health and decisionmaking.
- Support research to improve understanding of fertility intentions and sexual behaviors of women who are or whose partners are HIV-positive, and how fertility intentions are influenced by HAART; develop and evaluate accessible assisted reproductive technologies designed to assist in meeting fertility goals without HIV transmission.
- Conduct research to examine the consequences of HIV infection and treatment on women's and girls' access to, receipt of, and adherence to treatment for comorbid conditions, including other infectious and noninfectious diseases, substance abuse, and psychiatric illness.
- Examine the association between gender-specific physical and psychosocial consequences of HIV disease and HIV-related treatment initiation and maintenance.
- Develop and evaluate interventions to reduce adverse psychological, social, and economic consequences for women and girls infected or affected by HIV/AIDS, such as educational and economic opportunities, access to treatment and care, and prevention of violence and abuse.
- Conduct basic research to understand the dynamics of gender-specific stigma/discrimination associated with HIV/AIDS and to inform the development of structural interventions to reduce HIV/AIDS-associated stigma.

OBJECTIVE - G:

Identify and address the factors that influence women's and girls' access to and experience of HIV/AIDS-related research, care, support, treatment, and prevention services.

STRATEGIES:

- Support research to understand how the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care, reproductive health, family planning, and social services affect HIV risk behaviors, HIV transmission, and access to appropriate HIV care, support, treatment, and prevention services.
- Support research to develop effective strategies for the linkage, coordination, and integration of HIV care, support, treatment, and prevention services with primary medical care; drug, alcohol, and mental health treatment; STD services; reproductive health and family planning services; educational services; and community social services.
- Conduct research to examine transition of HIV/AIDS care across the lifespan, from pediatric to adolescent to adult care, and from adult to geriatric care, and develop interventions to optimize transition of care.
- Support research to understand the impact of policy and policy change—such as health care, health sector reform, health care financing systems, legislation, and regulations—on the delivery and utilization of HIV-related services, HIV risk behavior and transmission, and HIV/AIDS disease outcomes among women and girls.
- Encourage multidisciplinary research to identify unmet needs and elucidate barriers for women and girls to achieving optimal HIV care, support, treatment, and prevention services.
- Support research to study and address factors that influence the full participation of women and girls in HIV/AIDS-related research, including clinical trials for novel therapeutics and vaccines.
- Support research on effective strategies for disseminating products, findings, and information from HIV/AIDS-related research to women, girls, their communities, and policymakers.

OBJECTIVE - H:

Conduct and support research, training, and education on ethical issues specifically affecting women and girls in HIV/AIDS-related clinical, behavioral, epidemiological, and health care services research in different cultural settings.

STRATEGIES:

- Develop and evaluate efforts to educate women and girls who are potential trial participants about ethical and human rights issues in human research in advance of recruitment, with the goal of obtaining fully informed and free consent.
- Investigate the unintended consequences of policies and practices (including research practices) that provide special benefits to HIV-infected—as compared to uninfected and unaffected—women and girls (e.g., preferential treatment, health care benefits, access to medications, social services). Conduct research to examine and determine the contexts and factors that influence when the consent process is fully voluntary and is an informed aspect of the consent process.
- Investigate unintended harms and benefits that may accrue to women and girls, their families, and their communities as a result of participation in research studies.
- Examine the ethical risks and benefits of studies that involve treatment versus observation of women and girls.
- Investigate the ethical impact within a community of studies in which clinical trials provide the only access to therapeutics for women and girls.
- Assess potential negative and beneficial consequences for women and girls of conducting community-level epidemiological research.
- Study the ethical issues related to diagnostic and therapeutic strategies during pregnancy and lactation.
- Study the ethical issues related to breastfeeding and its alternatives.
- Study the ethical issues related to participation of women and girls in clinical trials.

FY 2007 OAR
Planning Group for
Women and Girls

FY 2007 WOMEN AND GIRLS PLANNING GROUP

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